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Editorial

# Surface Engineering of Liposomal Formulations for Targeted Drug Delivery

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## INTRODUCTION

Liposomes, basically including lecithin and cholesterol, are classic nanovesicles to treat some diseases clinically. As the first FDA approved nanomedicine, Doxil® (Doxorubicin HCl Liposome Injection) is a successful formulation to inhibit the development of some cancer and improve the life time of the patients after tumor surgery [1]. However, the non-specific accumulation of liposomes in Reticuloendothelial System (RES) impacts the normal function of uninvolved organs such as liver, spleen and bone marrow [2]. To improve the targeting of the liposomes, surface engineering of liposomes for controlled drug delivery has been widely investigated [3-6]. Small molecules such as sugar and folic acid were conjugated on the surface of liposomes to increase the uptake by cells [7]. Various ligands including proteins and peptides linked with artificial phospholipid in the bilayers of liposomes also greatly enhanced the affinities of carriers to the specific tissue [8,9].

Figure 1 illustrates the representative surface engineering strategies of liposomes for targeted drug delivery. Here, based on the current research in our lab, we summarize the advantages of surface engineering of liposomes and discuss different surface engineering techniques in details.

## PEG MODIFICATION

Normally, liposomes made of lecithin and cholesterol has shortcomings such as short circulating time due to quick removal by RES. However, long-circulating liposomes could be obtained by surface engineering. Poly (ethylene glycol) (PEG) modified liposomes (PEG-LIP), also known as stealth liposomes, significantly improve the pharmacokinetics behavior of vesicles [2]. After connection with PEG, the circulating time of liposomes in the blood vessels is extended while reducing uptake by mononuclear phagocytes. In tumor tissues, the structure of neovascularization provides right room for the PEG-LIP and facilitates the entry of liposomes across the vessels, which is called the Enhanced Permeability and Retention (EPR) effect. The PEG-LIP has stronger accumulation in the tumor tissue than LIP, which causes stronger elimination of tumor.

### Small molecules modification

Small molecules are connected with phospholipid and/or cholesterol in the bilayers of liposomes with or without linker. Hao et al. prepared mannose derivatives modified liposomes and investigated the distribution of carrier in the brain. Compared with non-modified liposomes, mannose derivatives were able to enhance the entry of liposomes into the brain parenchyma, indicating that the sugar facilitated the penetration of carriers across the Blood-Brain Barriers (BBB). Mannose is the substrate of Glucose Transporters (Glut)which expresses on the BBB and other brain parts [3]. In another study, Du et al. further investigated the mechanisms behind spatio-temporal distribution. Lentiviral vector was transfected into neural cells, including C6 glioma cell

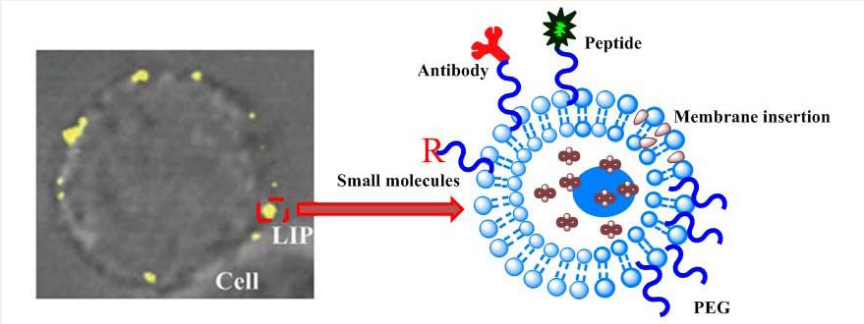


**Figure 1** Schematic illustration of various surface engineering of liposomes (reproduced with permission from reference [10] Copyright © 2010, Nature Publishing Group).

and PC12 pheochromocytoma cell, to enhance Glut expression. It proved that there was Glut expression-related enhancement of uptake after cells were incubated with mannose derivative modified liposomes (MAN-LIP) [4]. All the advantages of the previous studies in this topic were summarized and imagined with a bright prospect of MAN-LIP in the future [11].

Folic acid, a form of the water-soluble vitamin $B_9$, is often used for surface engineering to improve the targeting properties of liposomes. In tumor tissues, expression of folate receptor is always positively related to various malignancies [12]. Therefore, researchers utilized this phathophysiological phenomenon to achieve the targeted drug delivery of liposomes. Certainly, some tissues in the body, such as BBB, also highly express the folate receptors.This advantage can also be used to design the brain targeting liposomes to enhance the therapeutic efficacy [13]. However, the non-specific existence of the receptor impacts the targeting distribution of tumor-killing liposomes and causes the adverse effects in the clinical applications. Therefore, smarter strategies for surface modification of liposomes with small moleculesneed continuousdevelopments to balance the pros and cons of this system.

## Peptidemodification

The charge of liposomes can be regulated by surface engineering. The positively charged surface can enhance the uptake of liposomes by cells due to electrostatic attraction with negatively charged cell membrane molecules. TAT peptide, also known as a cell-penetrating peptide, is synthesized following *tat* gene in HIV-1. Unrestricted delivery of protein into cells could be achieved after TAT peptide modification. Torchilin et al. conjugated TAT peptide onto the surface of liposomes (TAT-LIP) enhancedthe uptake of liposomes bypassing the endocytotic pathway [14]. They incubated various cells including mouse Lewis lung carcinoma cells, rat cardiaomyocyte H9C2, and human breast tumor BT20 cells with TAT-LIP and confirmed the positive effects of TAT modification. TAT peptide consisting of several Arg amino acids in its chains may possess positive charge in the blood, which further increase the internalization of liposomes by targeted cells.

## Antibody modification

Antibody is a large Y-shape protein produced by plasma cells. It is used to conjugate onto the surface of liposomes to increase targeting efficiency to specific tissue. No matter what type of disease, cells normally produce some abnormal proteins or peptides, or leak some antigens in the foci. These antigens can be used to engineer the surface of liposomes. When heart suffers lower supplies of oxygen and/or blood, cardiomyocytes will die and leak some intracellular protein such as cardiac troponin (cTn). Cardiac troponin I (cTnI) was used as a specific marker to evaluate the damage of hypoxia in clinics. Liu et al. designed novel liposomes modified with cTnI and delivered oligonucleotides (AMO-1, the anti-miR-1 antisense oligonucleotides) to ischemic myocardium tissues [15]. The cTnIsurface modification enhanced accumulation of vesicle into the ischemic myocardium tissues which down-regulated the level of miR-1 after ligation. Meanwhile, the vesicles also reduced existence of the AMO-1 in other muscular tissues and inhibited the off-target of miR-1 owing to its specific affinities between anti-cardiac troponin I (anti-cTnI) antibody and its antigen. The ischemic myocardium targeting liposomes mainly existed in the cytoplasm but nucleus due to the anti-cTnI antibody modification.

However, antibody may stimulate immune system and induce the cytokine secretory. Sometime, the changed balance of immune system is beneficial to the invasion of diseases. There may be stronger stimuli to lymphocytes after conjugating antibody with artificial phospholipid. Therefore, if people want the antibody surface modified liposomes formulation from the bench to the bed side, a systematic evaluation of benefits must be performed.

## Membrane insertion

Except for conjugation on the surface, membrane insertion can also change the properties of liposomes for targeting therapy. Chemotherapy can't kill all the tumor cells, which causes tumor recurrence. Multiple Resistance Protein (MRP), as a pump, effluxes part of therapeutics out of the cells and gives cancerous cells an opportunity to survive. That's the reason why tumor cell possesses the multiple drug resistance. Drug inserted into the bilayer of liposomes acts on the MRP to inhibit pump functions and increase the concentration of chemotherapeutics in the cancerous cells. Tamoxifen possesses a similar structure of cholesterol and inhibit the activities of MRP. Shao et al. embedded tamoxifen into the phospholipid bilayer of liposomes and investigated the efficacy of liposomal daunorubicinon MCF-7/ADR-resistant human breast cancer cells [16]. They found that tamoxifen not only increased uptake of liposomal daunorubicin by cells, but improved the pharmaceutics kinetics of encapsulated drugs. In another research, Li et al. used two-compartment model to fit pharmacokinetic curve in rats [17]. The data further supported that tamoxifen extended the circulating time of drugs and enhanced the accumulation of liposomal daunorubicin. The increased cytotoxicity attributes to the increased drug concentration in the targeted cells and tumor tissues.

## Conjugation of cell with liposomes

T lymphocyte with rolling and homing virtues can serve as a cargo to deliver drug to the foci. Research has confirmed that the liposomes attachment on the cell can be used to eliminate the tumor. Stephen et al. hypothesized that liposomes linked with T lymphocyte can release some cytokine to mimic the sustained autocrine stimulation [10]. They conjugated liposome onto the surface of cells through reaction thiolending with maleimide head groups. The studies confirmed that conjugation increased the repopulation rate of hematopoietic stem cell grafts *in vivo* without influencing the cell function. Certainly, this platform can be used to deliver the therapeutics to treat some diseases.

## Perspective

Although the liposomes are not perfect carriers, the vesicles have served to treat various diseases. Compared with other nanoscale particles, the fabrication process of liposomes is simple and the stability of nanocarriers is excellent, especially after PEG surface modification. Different diseases need specific surface engineering solution. Current formulation of liposomes can't fix all the problems. With the development of new strategies and

novel techniques, smarter liposomes with fine controlled surface engineering will go into the clinical applications and improve the life quality of patients.

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